Poster 12: CYP Enzyme Induction by Cigarette Smoke Extract: An In Vitro Approach in Fresh and Cryopreserved Primary Human Hepatocytes

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Investigation of drug metabolism and drug-drug interactions is crucial in drug development, as emphasized by regulatory guidelines from the FDA, EMA, and ICH. Primarily responsible for drug metabolism are the cytochrome P450 (CYP) enzymes which are expressed in various organs of the human body, but most importantly in the liver [1]. Drug-drug interactions can occur when multiple substances are combined within a system, leading for example to a substance-mediated increase in CYP enzyme expression, which is known as induction [2]. Induction is a common phenomenon that can be caused by various agents, including cigarette smoke, which induces the CYP1A-family via the aryl hydrocarbon receptor (AhR) pathway [3]. Despite its relevance for drug-drug interactions, there is currently no in vitro model available to investigate CYP enzyme induction by cigarette smoke in the liver as key organ of metabolism.

This study developed and implemented an in vitro model using primary human hepatocytes to enable a comprehensive analysis of CYP enzyme induction by cigarette smoke extract (CSE)[#]. The model was inspired by regulatory guidelines, with emphasis placed on measuring mRNA expression via real-time qPCR and enzyme activity via LC-MS/MS of CYP1A1 [4] and CYP1A2. A robust induction of CYP1A1 and CYP1A2 by CSE was observed. Additionally, the induction of mRNA expression of CYP enzymes mediated by the pregnane X receptor (PXR) and constitutive androstane receptor (CAR) pathways was explored, with CYP2B6 and CYP3A4 also being induced by CSE. The stability of the induction model was verified in multiple donors of primary human hepatocytes with different donor demographics, including fresh and cryopreserved hepatocytes. The study demonstrated that CYP1A1 was highly inducible by CSE in all donors, suggesting a high interaction risk in cigarette smokers for drugs metabolized by CYP1A1. Furthermore, the study provides insights into the effects of donor variability on CYP enzyme induction by cigarette smoking, highlighting the importance of donor selection in in vitro models with primary cell cultures.

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